federal register

Wednesday
October 19, 1988

Part VI

Environmental Protection Agency

Regulation of Pesticides in Food: Addressing the Delaney Paradox Policy Statement; Notice

ENVIRONMENTAL PROTECTION AGENCY

[OPP-260052; -FRL-3388-3]

Regulation of Pesticides in Food: Addressing the Delaney Paradox Policy Statement

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This Notice announces a change in the position EPA will take in rulemaking proceedings under section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) concerning certain pesticides intended for use in food production. EPA's position will be that the section 409's so-called Delaney Clause—which, read literally, purports to bar absolutely the issuance of a food additive regulation for a food additive that has been found to induce cancer in test animals—is subject to a *de minimis* exception where the human dietary risk from residues of the pesticide is at most negligible. This change in position is intended to foster greater consistency in actions EPA will take with respect to the registrations of pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and tolerances for pesticide residues on food under sections 408 and 409 of the FFDCA. Elsewhere in this issue of the Federal Register, the Agency is proposing new procedural rules for establishing, modifying, and revoking section 409 food additive regulations, as well as procedural rules governing the filing of objections, requests for hearings, and the holding of hearings under sections 408 and 409. This Notice also discusses how EPA plans to approach the issue of what risks might be considered "negligible." This Notice provides the Agency's response to the recommendations of the recent National Academy of Sciences report entitled "Regulating Pesticides in Food: The Delaney Paradox". Public comment is invited on this Notice.

ADDRESS: Comments should bear the document control number "OPP-260052", and be submitted in triplicate to: Public Docket and Freedom of Information Section, Field Operations Division (TS-757C), Office of Pesticide Programs, Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: By mail: William L. Jordan, Policy and Special Projects Office, Office of Pesticide Programs (TS-766C), Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460. Office location and telephone number: Room 1115, CM #2, 1921 Jefferson Davis Highway, Arlington, VA, (703-557-7102).

SUPPLEMENTARY INFORMATION:

I. Introduction

The Environmental Protection Agency is responsible for regulating the sale and use of pesticide products under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), (7 U.S.C. 136 *et seq*). FIFRA contains a standard for registration that allows EPA to take both the risks and the benefits of a pesticide's use into account.

The Agency also regulates pesticide residues on food under sections 408 and 409 of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 346a, and 348). Food is "adulterated" and subject to seizure under the FFDCA if it is found to bear pesticide residues that are not permitted by appropriate section 408 and 409 tolerances. Section 408 of the FFDCA, like the FIFRA, gives the Agency authority to balance risks and benefits in reaching regulatory decisions with respect to pesticide residues on raw agricultural commodities section 409 of the FFDCA governs the establishment of food additive regulations (often called 409 tolerances) in processed food and feed. EPA interprets section 409 to also allow EPA to consider benefits to food consumers in reaching its decisions unless the Delaney Clause applies. However, the Delaney Clause of section 409, if read literally, is a risk-only standard that bars the establishment of any food additive regulation that would authorize residues in or on processed food or feed of any pesticide that has been found to induce cancer when ingested by man or test animals, with certain limited exceptions.

The difference in the standards of these two statutes presents EPA with a major problem in regulating certain pesticide chemicals which have been found to induce cancer in test animals. Such pesticides may be ineligible for food additive regulations under the FFDCA even if they have been found to pose no unreasonable risk to humans and qualify for registration under FIFRA. This problem may arise in three situations: (1) When a food additive regulation is sought for a new pesticide chemical (or a new use of a currently registered chemical) that induces cancer in animals; (2) when new residue data indicate a need for a food additive regulation for a registered pesticide known to induce cancer in animals; or (3) when new toxicity data show that a registered pesticide for which food additive regulations have been established induces cancer in animals.

In the first situation, the issue is whether to allow the pesticide to enter the market or to be marketed initially for a particular food use. EPA's current regulations prohibit FIFRA registration until the issuance of any needed tolerances and food additive regulations associated with the pesticide's use. The second and third situations require EPA to decide whether to make unlawful the marketing of a pesticide for those previously-approved food uses subject to section 409. The number of uses in these latter two categories is increasing as EPA receives more and more toxicity and residue data. Of significant concern are the differences in the standards now applied to old and new pesticides. Under current Agency practice, as described more fully later in this Notice, a new pesticide that poses a relatively low risk of cancer may be barred from registration because of Delaney Clause constraints, while an old pesticide that poses a higher risk and that is used for the same purposes might remain on the market.

To address these issues, in February 1985 the Agency commissioned the Board on Agriculture of the National Research Council/National Academy of Sciences ("NAS") to examine the impact of the Delaney Clause on the tolerance-setting process and on EPA decision-making. The NAS committee formed to conduct this study included experts in agricultural pest control, pesticide development, agricultural economics, cancer risk assessment, public health, food science, regulatory decision making, and law.

The detailed report prepared by the NAS, entitled "Regulating Pesticides in Food: The Delaney Paradox," was issued on May 20, 1987. The report set forth four main recommendations:

1. Pesticide residues in food, whether marketed in raw or processed form or governed by old or new tolerances, should be regulated on the basis of consistent standards. Current law and regulations governing residues in raw and processed foods are inconsistent with this goal.

2. A negligible risk standard for carcinogens in food, applied consistently to all pesticides and to all forms of food, could dramatically reduce total dietary exposure to oncogenic pesticides with modest reduction of benefits.

3. EPA should focus its energies on reducing risk from the most worrisome pesticides on the most-consumed crops.

4. The EPA should develop improved tools and methods to more systematically estimate the overall

impact of prospective regulatory actions on health, the environment, and food production.

The Agency has evaluated the recommendations of the NAS, and as discussed later in this document, has reached conclusions about what would be an ideal policy, one that would be based on the NAS recommendations. In summary under this ideal policy, the Agency would apply a uniform set of criteria to all FIFRA registration decisions and all FFDCA section 408 tolerance and section 409 food additive regulation decisions. If a pesticide's use would pose no risk or only a negligible risk, the pesticide's use would be approved under both Acts without any particular scrutiny of benefits. This has for some time been EPA's practice with respect to decisions on pesticides that pose only non-cancer risks, and with respect to decisions under FIFRA and under FFDCA section 408 on pesticides that may pose cancer risks. (EPA has assumed that an applicant's willingness to expend the sums required to obtain registration of a pesticide, in the expectation of recovering those sums by sales of the pesticide, indicates that the pesticide's use will yield benefits that are greater than negligible.) Under the ideal policy, registrations and the associated tolerances and food additive regulations similarly would be granted for pesticides that pose at most a negligible risk of cancer to humans (and meet the other requirements of FIFRA and the FFDCA). For those pesticides deemed to pose a greater-than-negligible risk, a risk/benefit evaluation would determine the appropriateness of FIFRA registration and FFDCA clearances under sections 408 and 409. The greater the degree of risk, the greater the benefits that would have to be shown to justify approval, and the more intensive would be the benefits evaluation required to reach a regulatory decision.

Implementation of this ideal policy, however, is subject to the constraints imposed by the Delaney Clause. In the case of a use of a pesticide that requires a section 409 clearance and that poses a cancer risk that is greater than negligible, the Delaney Clause ordinarily bars approval of the use; the Agency is unaware of any legal theory that would justify a change in its current practice of refusing to issue new food additive regulations in such situations (with certain exceptions discussed in detail later in this Notice). However, for pesticides that pose at most a negligible risk of cancer and whose use requires section 409 clearances, EPA will change its current practice to the extent that, in the future, EPA will propose to issue food additive regulations on the basis of the *de minimis* doctrine, described in Unit II of this Notice.

The Agency wishes to make it clear that the interpretations and policy changes it is announcing today have no final effect with respect to any individual pesticide. This Notice relates primarily to the regulatory treatment of some pesticides under FFDCA section 409. Any food additive regulation that EPA may issue in reliance on the *de minimis* doctrine discussed in this Notice will be preceded by issuance of a proposed rule, and also will be referred to the FIFRA Scientific Advisory Panel. Section 409(b) and 409(h) allow "any person" to petition EPA to issue, modify, or revoke a section 409 food additive regulation, and section 409(c) says that EPA must act on such a petition. Under section 409(f), any "adversely affected person" (a term that has been given a very inclusive reading by the courts) may object to an EPA action taken either in response to a section 409(b) petition or at EPA's own initiative under section 409(d). EPA must rule on the objection; if factual matters are at issue, EPA first must hold a formal evidentiary hearing to produce a record upon which the ruling must be based. Although this Notice sets forth positions that the Agency expects to take initially in relevant proceedings arising under FFDCA section 409, EPA decisional officials will be open to all arguments presented in those proceedings and will base their final decisions on the merits of the arguments presented. See *McLouth Steel Products Corp. v. Thomas,* 838 F. 2d 1317 (D.C. Cir. 1988). Judicial review of rulings on individual objections under FFDCA section 409 is available only in the manner described by section 409(g). EPA will take the position that this Notice is not itself properly the subject of judicial review because it lacks the requisite finality.

A detailed discussion of the policy changes involved is set forth in Unit III. of this Notice.

II. Legal and Regulatory Background

EPA often must apply four different and sometimes conflicting statutory standards in deciding whether a particular pesticide may be used in food production: one under the FIFRA and three under the FFDCA.

A. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

The sale, distribution, and use of pesticides in the United States are governed directly by the FIFRA and are also influenced heavily by the FFDCA. FIFRA requires that all pesticides which are sold or distributed in the United States be registered in accordance with the statutory standard for registration set forth in FIFRA. That standard requires, among other thing, that the pesticide perform its intended function without causing "unreasonable adverse effects on the environment." (FIFRA section 3(c)(5)). The term "unreasonable adverse effects on the environment" is defined as "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide," (FIFRA section 2(bb)). Under FIFRA section 6, EPA may cancel the registration of a use of a pesticide [1] (or require modifications in the terms and conditions of registration in lieu of cancellation) if the Agency determines that the risks of use of the pesticide outweigh the benefits of the use.

EPA regulations (40 CFR 162.7(d)(2)(iii)(E)) and 162.167(a)(4), redesignated as 40 CFR 152.112, 152.113, and 152.114, see 53 FR 15952, May 4, 1988) provide that a registration may not be granted if "the intended use of the pesticide results or may reasonably be expected to result, directly or indirectly, in residues of the pesticide becoming a component of food or feed," unless the necessary sections 408 and 409 clearances have been issued.

This requirement assures that a pesticide use will not be registered for a food crop unless the Agency has determined that the resulting pesticide residues in or on the crop will not exceed a safe level. Moreover, by examining the pesticide use under the statutory scheme as a whole and assuring that the criteria of both FIFRA and FFDCA are met, the Agency avoids the potential for residues that are illegal under the FFDCA appearing in or on foods as a result of pesticide use that is legal under FIFRA. It has been EPA's belief that pesticide users and food processors should be able to safely assume that a pesticide registered under FIFRA has the appropriate clearances under the FFDCA for the food uses listed on the FIFRA label.

B. Sections 408 and 409 of the Federal Food, Drug and Cosmetic Act (FFDCA)

Under FFDCA section 402, a raw agricultural commodity is adulterated if

[1] The decision to cancel a pesticide can result from a Special Review, an intensive review of the risks and benefits of a pesticide which meets or exceeds risk criteria set forth in 40 CFR Part 154. The Agency also can take action to cancel (and, if necessary, to suspend during the cancellation proceedings) the registration of a pesticide whose risks appear to exceed its benefits, without first going through the Special Review process.

it contains a pesticide residue not authorized by a FFDCA section 408 tolerance (maximum permissible level) or an exemption from the requirement of a tolerance. An adulterated commodity sold or distributed in interstate commerce is subject to seizure by the Food and Drug Administration (FDA).[2]

To establish a tolerance or exemption regulation under section 408, the Agency must find that the regulation would "protect the public health." (FFDCA section 408(b)). In reaching this determination, the Agency is directed to consider, among "other relevant factors," the necessity for the production of an adequate, wholesome, and economical food supply, and the other ways in which the consumer may be affected by the pesticide. Thus, in the Agency's view, section 408 of the FFDCA expressly gives the Agency the authority to balance risks against benefits in determining appropriate tolerance levels.

Under FFDCA section 402, food is adulterated (and hence subject to seizure) if it contains any food additive (including any pesticide residue) not authorized by a section 409 food additive regulation. An important exception to this provision is that a processed food containing pesticide residues resulting from the "carryover" from treatment at the raw agricultural commodity stage is not regarded as adulterated if the residue level in such a food is no greater than that allowed by the section 408 tolerance established for the raw agricultural commodity.

The establishement of a food additive regulation under section 409 requires a finding under the "general safety clause" in section 409(c)(3) that the use of the pesticide "will be safe." The only direct guidance given by the Act as to the meaning of the term "safe" is that the term "has reference to the health of man or animal," (FFDCA section 201(u)). Factors to be considered in making this "general safety clause" determination are (1) the probable consumption of the pesticide or its metabolites; (2) the cumulative effect of the pesticide in the diet of man or animals, taking into account any related substances in the diet; (3) appropriate safety factors to relate the animal data to the human risk evaluation; and (4) "other relevant factors." FFDCA Section 409(c)(5)).

Appendix A contains a discussion of the procedures followed by the Agency in evaluating safe residue levels for tolerances and food additive regulations.

The general safety clause in section 409(c)(3) has been construed by the Agency to allow the weighing of benefits and risks when issuing food additive regulations. The legislative history indicates that section 409 was intended to permit the use of food additives "which may benefit our people and our economy when the proposed usages of such additives are in amounts accepted * * * as safe," and that "the test which should determine whether or not a particular additive may be used in a specific percentage of relationship of the volume of the product to which it might be added should be that of reasonable certainty in the minds of competent scientists that the additive is not harmful to man or animal." (S. Rep. No. 2422, 85th Cong. 2d Sess., August 18, 1958, at 2–3). In EPA's view, the determination of whether use of a pesticidal food additive is "not harmful" or is "safe" should take into account the net effects of use of the additive on the food supply, including the benefit (or to put it another way the avoidance of harm) to an adequate, wholesome, and economical supply of food that may result from a pesticide's use as well as any harm to the food supply that may result from the pesticide's use. At least for residues of pesticide chemicals, EPA believes that this kind of benefit should be regarded as one of the "relevant factors" EPA may consider under FFDCA section 409(c)(5), even though it is not listed specifically there as it is in section 408(b). A risk/benefit reading of the general safety clause also was adopted by the one court that has addressed the issue.[3] FDA, however, has tended to interpret the section 409 general safety clause as a criterion that focuses solely on the risks to the food supply caused by the food additive, as opposed to the risks avoided, and this view has considerable support in the legislative history of section 409 and in scholarly journals.

C. The Delaney Clause

The one clear exception to the Agency's latitude to balance risks and benefits for food additives under section 409 is the "Delaney Clause" in section 409(c)(3). The Delaney Clause states that a food additive shall not be deemed safe "if it is found to induce cancer when ingested by man or animal or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." Because FFDCA section 408 contains no counterpart to the Delaney Clause, the Agency has the authority to evaluate the risk posed by the presence of residues of a carcinogenic pesticide in a raw agricultural commodity, and to establish a section 408 tolerance at a level which will protect the public health, taking benefits to the food supply into account. As long as the processed food does not contain residues above the level allowed in the raw agricultural commodity, residues of that carcinogenic pesticide may legally be present in such processed food. However, where residues of the chemical concentrate above the section 408 tolerance level during processing, or result from use of a pesticide during or after processing, a food additive regulation might not be appropriate because of the Delaney Clause bar. The Delaney Clause contains an express exception (the "DES provisio") that allows a carcinogenic ingredient of animal feed to be found "safe" if such ingredient will not adversely affect the animal and if "no residue" of the substance will be found, by an Agency-approved method, in any edible food yielded or derived from the treated animal. FDA has concluded that the provision should be implemented by a "sensitivity-of-method" approach that allows a carcinogenic ingredient to be added to animal feed if "no residues" of that ingredient are detectable by an FDA-approved analytical method that is sensitive enough to detect any level of residue representing a lifetime excess human cancer risk of more than one in a million (44 FR 17070).[4] The FDA

[2] Under Reorganization Plan No. 3 of 1970, which established EPA, the authority to set tolerances for pesticide chemicals in raw agricultural commodities and processed food under FFDCA sections 408 and 409 respectively, was transferred from FDA to EPA. FDA enforces most of the pesticide tolerances and food additive regulations that EPA issues, along with the many non-pesticide food additive regulations that FDA issues. The U.S. Department of Agriculture enforces the tolerances and food additive regulations with respect to meat, poultry, and egg products.

[3] In *Continental Chemiste Corp.* v. *Ruckelshaus*, 461 F.2d 331, 340–341 (7th Cir. 1972), a case dealing with the relationship of FIFRA and FFDCA, the court stated that "[t]he test of safety [contained in the general safety clause of section 409] was intended to take into account the broader concepts of safety under the intended conditions of use; the benefits of the additive were to be evaluated rather than merely its potential for harm. In short, in making its ultimate determination whether new additives, or food containing them, may be marketed, [the FFDCA] employs the kind of substantive standard of product safety embodied in [the pre–1972] FIFRA's injury to man' concept, rather than a narrow consideration of the character of the additive itself." In discussing this "injury to man" concept, the court noted that "the substantive standards, phrased in terms of protection of the public and impact on living man, require consideration of the aggregate effect of a product's use upon the environment, including not only its potential for harm, but also the benefits which would be lost by removing it from the market." *Id.* at 336.

[4] FDA has analyzed the meaning of the DES proviso in proposed regulations published in the

Continued

approach incorporates a series of conservative assumptions for calculating the allowable residue levels in individual food items and in the total diet.

EPA has used the sensitivity-of-method approach in two actions establishing food additive regulations, one concerning thiodicarb and its possibly oncogenic metabolite acetamide on the animal feeds cottonseed hulls and soybean hulls (50 FR 27452, July 3, 1985; 50 FR 41341, October 10, 1985), and another concerning cyromazine and its possibly oncogenic metabolite melamine in or on poultry feed (49 FR 18120, April 27, 1984; 50 FR 20370, May 15, 1985).

If the chemcial induced cancer in animal studies in which the route of exposure was other than ingestion, the Delaney Clause by its own terms applies only if the tests in question "are appropriate for the evaluation of the safety of food additives." The Agency thus has discretion to decide whether a test showing cancer induction as a result of, e.g., dermal exposure to a chemical is "appropriate" for Delaney Clause purposes.

Two administratives doctrines, the "constituents policy" and the *de minimis* approach, also in EPA's view allow the establishment of food additive regulations in appropriate situations. The "consituents policy," developed by FDA, relies on the fact that the prohibitory language of the Delaney Clause pertains to any food additive, that has been shown to induce cancer in animals, but does not bar approval where an unwanted impurity (a "constituent") of the additive, tested by itself, is found to induce cancer. Thus, under the constituents policy, a food additive regulation may be established if the food additive as a whole does not cause cancer, even though the additive contains an undesired, nonfunctional constituent which is itself a carcinogen. In this situation, the impurity is judged under the general safety provisions of the applicable section of the FFDCA, using risk assessment as one of the decision-making tools. The Sixth Circuit Court of Appeals has upheld FDA's use of the constituents policy to interpret the color additives Delaney Clause provision in section 706(b)(5)(B) of the statute. (*Scott v. FDA*, 728 F. 2d 322 (6th Cir. 1984)). This provision contains a prohibition closely similar to that found in the section 409 Delaney Clause.

EPA has used the constituents policy in a rulemaking establishing a food additive regulation for dicamba in sugarcane molasses. Dicamba itself is not thought to be oncogenic; however, the pesticide formulation contains small amounts of a carcinogenic nitrosamine contaminant. EPA found the potential risk attributable to the presence of this contaminant to be very small, i.e., with an upper limit in the 10^{-9} range. Accordingly, the agency concluded that the requirements of section 409 were satisfied. (48 FR 11119, March 16, 1983; 48 FR 34024, July 27, 1983; 48 FR 50528, November 2, 1983).

In discussing its use of the "constituents policy" approach for dicamba, EPA noted that it does not regard deliberately added active or inert ingredients, or metabolites thereof, as potential candidates for clearance under the constituents policy. Rather, the Agency said it would only consider applying the rationale to unwanted impurities resulting from the manufacture of the pesticide (intermediates, residual reactants, products of side reactions, and chemical degradates). Furthermore, the Agency said that it would consider using this rationale in issuing a food additive regulation only where the potential risk from the impurity is extremely low, and that in estimating this risk, the Agency would rely on very conservative risk estimation methodology. (48 FR 34024, July 27, 1983).

Finally, the *de minimis* approach derives from case law holding that an administrative agency ordinarily has the inherent authority to avoid applying the terms of a statute literally when to do so would yield pointless results.[5] Two conditions are necessary to allow an agency to invoke the *de minimis* doctrine. First, the problem that would be addressed by regulation must be trivial in fact, such that no real benefit would result from regulation. Second, the legislative design must allow the Agency not to apply the statute literally in such a case.

In a recent case addressing the Delaney Clause contained in the color additive provisions of the FFDCA enacted in 1960 (*Public Citizen* v. *Young*, 831 F.2nd 1108 (D.C. Cir. 1987), cert. denied, 108 S.Ct. 1470), FDA argued that the establishment of a *de minimis* exception to the Delaney Clause is consistent with the legislative design, and that conservatively-assessed risks of one in a million (10^{-6}) or less should be regarded as trivial and thus subject to the exception. FDA relied on legislative history indicating that the Delaney Clause should be applied in a reasonable way. But the court rejected FDA's argument that the legislative history of the FFDCA color additive provisions does not preclude the use of the *de minimis* exception. The court held that "the Delaney Clause of the Color Additive Amendments does not contain an implicit *de minimis* exception for carcinogenic dyes with trivial risks to humans" because "Congress adopted an 'extraordinarily rigid' position, denying the FDA authority to list a dye once it found it to 'induce cancer in * * * animals'." (831 F.2nd at 1122). In the court's view, the proper mechanism for obtaining relief from the Delaney Clause with respect to color additives whose risk is trivial is to request that Congress make appropriate modifications to the statute. The food additive Delaney Clause in section 409, adopted in 1958, was not at issue in the case. Indeed, the court noted that the context of the section 409 provision was entirely different from that of the color additive Delaney Clause, and that "the operation of the food additive Delaney Clause raises complex issues distinct from those of this appeal" (id. at 1120, 1118 n. 13). The court suggested, moreover, that the legislative history of the section 409 Delaney Clause might lead to a different result (id. at 1120).

The Delaney Clause has long been regarded as allowing the administering agency to exercise scientific judgment and discretion in deciding whether a food additive "induces cancer" in animals.[6] EPA has generally assumed that, for purposes of the Delaney Clause, a substance "induces cancer" in animals if, in a well-conducted animal feeding study, a statistically significant increase in the incidence of histologically related tumors (benign, malignant, or combined)

Federal Register of March 20, 1979 (44 FR 17070), and February 11, 1983 (48 FR 6361). FDA's final rule establishing procedures implementing this sensitivity-of-method approach was published on December 31, 1987 (52 FR 49572).

[5] See *Alabama Power Co.* v. *Costle*, 636 F.2d 323, 360 (D.C. Cir. 1979); *District of Columbia* v. *Orleans*, 406 F.2d 957, 959 (D.C. Cir. 1968); *Environmental Defense Fund, Inc.* v. *EPA*, 636 F.2d 1287, 1284 n. 46 (D.C. Cir. 1980).

[6] See, e.g., the 1960 statement by Arthur S. Fleming, Secretary of Health, Education and Welfare, that the Delaney Clause "allows the Department and its scientific people full discretion and judgment in deciding whether a substance has been shown to produce cancer when added to the diet of test animals," cited with approval in the Report of the House Committee on Interstate and Foreign Commerce on the Color Additive Amendments of 1960 (H.R. Rep. No. 1761, 85th Cong. 2d Sess., June 7, 1960) at 14. See also the May 1960 report of the President's Science Advisory Committee, noting that "[t]he definition of a carcinogen implicit in the language of section 409(c) requires discretion in its interpretation because so may variables enter into a judgment as to whether a particular substance is or is not carcinogenic," cited with approval in the Senate floor debate on reconsideration of the Delaney Clause in the Color Additive Amendments of 1960. Congressional Record 15380 (July 1, 1960).

BEST COPY AVAILABLE

is observed in treated animals compared to concurrent control animals, unless there is a reason to conclude that the observed increase is unrelated to the ingestion of the test substance. Under this approach, a pesticide may be found to "induce cancer" in animals despite the fact that increased tumor incidence occurs only at high doses, or that only benign tumors occur, and despite negative results in other animal feeding studies. FDA has taken a similar approach in assessing data for the purposes of the Delaney Clause.[7]

There is at least "limited evidence" of carcinogenicity (virtually all from animal studies) for 66 or more of the approximately 350 food-use pesticides already approved for use, under the classification scheme set forth in EPA's "Guidelines for Carcinogen Risk Assessment," (51 FR 33992, September 24, 1986), described in Appendix A. EPA expects this number to become somewhat larger as it receives and evaluates more studies on the food-use pesticides.[8] A substantial portion of these pesticides require section 409 food additive regulations for one or more of their uses. Appendix B lists those pesticides which currently have been identified by the Agency as potential carcinogens and indicates which ones have, or have recently been determined to need, section 409 food additive regulations.

D. Current Policy Has Been Constrained by the Delaney Clause

From the foregoing discussion, it is apparent that if EPA determines that a pesticide poses a cancer risk that is greater than negligible and that outweighs the pesticide's benefits, the pesticide's FIFRA registration should be cancelled and its FFDCA sections 408 and 409 clearances should be revoked. There is no conflict between the various standards in such a case, and EPA's current practice reflects this lack of conflict.

Difficulties arise in the two remaining situations. A pesticide may pose only a negligible cancer risk, or it may pose a cancer risk that is greater than negligible but nonetheless is not so great as to outweigh the pesticide's benefits to the food supply. In both of the latter situations, EPA views FIFRA, FFDCA section 408, and FFDCA section 409's general safety clause as allowing the registration or continued registration of the pesticide and the issuance or continuation of needed FFDCA clearances. But the Delaney Clause of FFDCA section 409 arguably bars the issuance of new section 409 clearances for pesticides in either of the latter two situations, and thus concomitantly calls into question the status of such pesticides under FFDCA section 408 and FIFRA. Due to the constraints dictated by the literal approach to the Delaney Clause, the Agency has not been willing to register a carcinogenic pesticide for a new food use which requires a section 409 food additive regulation, even though that pesticide meets the risk/benefit standards in the other statutory provisions. And since there is often no practical way to assure that the raw agricultural commodity at issue will not be processed, the Agency generally does not grant a section 408 tolerance for residues of the pesticide on a raw agricultural commodity in a situation where an associated section 409 food additive regulation is needed but cannot be issued. As noted earlier, EPA's regulations currently provide that before a pesticide may be registered under FIFRA for a food or feed use, there must exist appropriate clearances under FFDCA sections 408 and 409 for the pesticide residues.

However, if the pesticide is to be used on a type of raw agricultural commodity which is not processed or if concentration of the raw-commodity residues does not occur during processing, and if the pesticides is not added during or after processing, no food additive regulation is needed. If the pesticide use passes the risk/benefit test under FIFRA and FFDCA section 408, a registration can be granted. This is true even if the estimated dietary cancer risk to the public is the same as or higher than the risk posed by an analogous pesticide use for which a food additive regulation is required. Thus, very similar risk situations have been treated quite differently because of the inconsistent statutory provisions. This approach has not necessarily resulted in lower health risks for the public. In fact, there is a strong argument that in some cases the constraints of the Delaney Clause paradoxically may have led to greater risks to the public. New pesticides that pose lower cancer risks than pesticides currently on the market have been denied registration while older, more hazardous pesticides remained in use.

The Agency's treatment of established food additive regulations for registered pesticide chemicals shown by new data to induce cancer in test animals has been quite different than the just-described treatment of requests for new food additive regulations. To date, the Agency has not taken action based on the Delaney Clause to revoke established food additive regulations. In many instances, taking such action would require EPA either to revoke the associated 408 tolerances and cancel the FIFRA registration (despite the risk/benefit criteria that would govern such actions), or to abandon its long-standing policy that the lawful application of a pesticide should not result in illegal pesticide residues. Many of these pesticides appear to pose low or negligible risks and to have substantial benefits for the production of food in this country.

The Agency has deferred action in such cases, while studying the dilemma posed by the statutory scheme. Section 409(h), which authorizes EPA to issue regulations establishing procedures for amending or repealing food additive regulations, does not expressly require repeal of food additive regulations when new data indicate that the pesticide induces cancer.[9] The Agency arguably has the latitude to assess the safety of established food additive regulations under any standard it chooses to adopt that is not arbitrary and capricious within the meaning of the Administrative Procedure Act; it arguably could adopt a standard based on the general safety clause of section 409(c)(3), or on a non-FFDCA standard, such as the FIFRA risk/benefit standard.

[7] See 52 FR 49572, 49577 (December 31, 1987) for a statement of FDA's current policy. See also 51 FR 28331, 28340 (August 7, 1986), where FDA specifically noted that "any chemical shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen." The evidence as a whole may lead FDA to conclude that a substance that only causes benign tumors should be regulated as a carcinogen under the Delaney Clause. (52 FR 49577, December 31, 1987). However, a finding of only benign tumors does not of necessity lead FDA to conclude that the chemical "induces cancer" under the Delaney Clause.

[8] In recent years, the Agency has been conducting a systematic review of currently registered pesticides under the Registration Standards process. This review determines the sufficiency of the data base for these chemicals in light of current data requirements, and evaluates the current terms of registration to see if modifications are appropriate. During the development of a Standard, data gaps are identified and data call-in notices sent to registrants pursuant to FIFRA section 3(c)(2)(B), which gives the Agency authority to require the submission of data necessary to support existing registrations. The Agency evaluates the adequacy of existing tolerances and food additive regulations for chemicals registered for food uses during the Registration Standard review. Appendix C lists those food use pesticides for which Registration Standards have been developed or are scheduled for FY 1988.

[9] Section 409(h) states: "[The Administrator] shall by regulation prescribe the procedure by which regulations under (section 409) shall be amended or repealed, and such procedure shall conform to the procedure provided in this section for the promulgation of such regulation." The interpretation that revocation is not expressly required is based on giving the term "procedure" its normal meaning, rather than reading into the term the substantive criteria of section 409.

Thus, the Agency could conclude that a previously-approved use of a pesticide is "safe" or not "unreasonable," even though the potential risk is greater than "negligible," if the benefits of the use to the food supply outweigh its risks. On the other hand, if the Agency concluded that the presence of residues in the processed food or feed posed a risk that is "unreasonable" within the meaning of FIFRA or not "safe" within the meaning of the general safety clause of FFDCA section 409, considering the balance of risks and benefits, the Agency would be under an obligation to take action to repeal the regulation (or, in appropriate situations, to amend the regulation to allow a lower residue level determined to be "safe" or "reasonable") and to cancel or modify the terms and conditions of the related FIFRA registration as necessary to assure that the use of the pesticide did not cause unreasonable adverse effects on the environment. This approach would allow EPA to reconcile the FIFRA and FFDCA standards.

The contrary argument would rest on the assumption that Congress must have intended any reevaluation of an existing food additive regulation to be based on the section 409(c) criteria for establishing new regulations, and that the Delaney Clause is an integral part of section 409(c). This view of section 409 thus would incorporate section 409(c)—including the Delaney Clause—into section 409(h) of the statute. Under this reading, a food additive regulation would have to be revoked if new information should indicate that the Delaney Clause would have barred issuance of the regulation had that information been available originally.[10]

Such an approach might result in the cancellation of pesticide registrations for uses that meet the risk/benefit standard of FIFRA, FFDCA section 408, and FFDCA section 409's general safety clause, but that cannot conform to the risk-only, zero-risk standard of the Delaney Clause. Once the food additive regulation had been repealed, the presence of residues of that pesticide in the processed food in question would be illegal under the FFDCA, and the wisdom of allowing the pesticide to be sold under the FIFRA registration for use in producing that food would be questionable. To be consistent, many related section 408 tolerances also would have to be repealed under this approach, because such tolerances arguably would be inappropriate where residues could concentrate during processing to an unapproved level higher than the tolerance for the raw agricultural commodity. This approach, carried to its logical conclusion, might end many valuable uses of pesticide chemicals and might result in significant adverse consequences to food production, while resulting in little or no risk reduction. It should be noted that a registrant of a pesticide faced with a proposed FIFRA cancellation based entirely or primarily on the fact that the pesticide's residues are not thought to be "safe" within the meaning of FFDCA section 409 might assert that a FIFRA cancellation cannot be based on criteria imported from the FFDCA, and might succeed (see *Continental Chemists Corp.*v. *Ruckelshaus*, 461 F. 2d 331 (1972)). If the approach described in this paragraph were successful, however, there again would be no dichotomy in the treatment of old and new pesticides.

The system that has been used by EPA so far has the added undesirable feature of placing new pesticides that are barred from registration because of the strict reading of the Delaney Clause at a disadvantage relative to old products that are shown by new data to pose comparable or higher risks. Given the high costs of data development, there is little incentive to develop a new food use pesticide that shows carcinogenic potential—even if the risk it would pose would be minimal, and even if it could replace an old product that poses a higher risk—if initial registration is likely to be barred by Delaney Clause considerations. Thus, the development of new, lower-risk chemicals to replace old, higher-risk pesticides may have been retarded by the Agency's past implementation of the Delaney Clause.

A reassessment of the data in support of the tolerances for a particular pesticide chemical may present another serious concern. The data review by the Agency may reveal, with respect to a chemical that induces cancer in animal studies, that not all the necessary section 409 tolerances are in place. New residue data or a new review of old data may lead the Agency to determine that residues concentrate during processing and that section 409 food additive regulations have not been promulgated to cover this situation. If the Agency cannot promulgate such regulations because of the Delaney Clause ban, these processed commodities would contain illegal residues and would be subject to seizure by FDA. To prevent the presence of these residues in the processed commodities, the Agency would have to attempt to revoke the corresponding FIFRA registrations and FFDCA section 408 tolerances (unless appropriate use restrictions on the pesticide labeling could be developed to prevent the use of the pesticide on commodities destined for processing). Such action could profoundly limit the use of many beneficial pesticide chemicals.

The Agency is facing the issues discussed here with an ever-increasing number of old pesticide chemicals. (Appendix D discusses certain examples of pesticide chemicals currently or recently under review which give an overview of the practical dimensions of the problem.) EPA's decision on whether to attempt to apply the section 409(c) criteria retrospectively under section 409(h) may depend on whether its approach to negligible-risk situations, set forth in unit III of this document, is upheld.

E. Potential for Legislative Solution

The administrative approaches discussed so far in this document would solve only some of the problems the Agency faces in this area. Moreover, implementing those approaches will be controversial and might involve the Agency in protracted litigation that could cause uncertainty and make it difficult for businesses to make plans about pesticide development and pesticide use. A legislative solution, stating clearly that the Agency has the authority to grant food additive regulations for pesticide residues posing at most a negligible risk, clearly would be desirable. Additional legislative changes would be required to allow the Agency to fully reconcile FFDCA and FIFRA. Such legislation ideally would give the EPA the latitude to establish tolerances and food additive regulations for pesticides under a risk/benefit standard compatible with FIFRA, with a definitive statement that clearances for both raw and processed foods are to be established under a risk/benefit approach.

Hearings have been held recently in the House of Representatives on two bills that would address these issues. H.R. 4739, introduced by Congressman Waxman, would provide for the regulation of pesticide residues exclusively under comprehensively rewritten FFDCA section 408; H.R. 4937, introduced by Congressmen Brown and Roberts, would also provide for regulating pesticide residues under section 408, but would make only minor changes in the substance of that section.

[10] FDA appears to interpret the Delaney Clause as applying to food additives established prior to any indication of carcinogenic effect for such chemicals. See, for example, the discussion in the proposed FDA determination not to ban the use of methylene chloride in decaffeinated coffee (50 FR 51551, 51555 December 18, 1985).

III. Response to First and Second NAS Recommendations

A. Introduction

The Agency agrees completely with the NAS Report's most important conclusion—that a consistent approach ideally should be followed in the regulation of pesticides for food uses, regardless of whether the pesticides are new or old or whether the foods are raw or processed. As the NAS Report points out, there is no scientific reason to regulate pesticide residues in raw commodities differently from those in processed commodities. For risk assessment purposes, what is critical is not the type of food or feed commodity on which residues are present, but rather the identity and magnitude of the residues in the food and the associated consumption pattern. Likewise, EPA agrees with NAS that pesticides should be regulated consistently whether they are newly developed or have been on the market for many years.

Use of regulatory criteria that reflected those two NAS recommendations would allow the Agency to regulate high-risk pesticides more stringently than those that pose low risks, and permit the registration of new pesticides that offer substantial benefits and pose relatively insignificant risks. Riskier pesticides could then be replaced, and the total dietary risk reduced, with only minor adverse impacts on food production. This approach would be eminently sensible and desirable.

B. Policy for Achieving Greater Consistency in Evaluating Pesticides Under FIFRA and the FFDCA

The Agency believes that the most desirable way to achieve consistency in regulating potentially carcinogenic food-use pesticides would be to evaluate them under the same risk/benefit standard for both registration and tolerance purposes. However, if a section 409 regulation is required for a chemical to which the Delaney Clause applies, EPA believes that current law allows this approach to be used only to the extent that the *de minimis* doctrine allows Delaney Clause considerations to be dismissed. The following Table I outlines the regulatory outcomes that EPA would propose in response to various types of findings with respect to the cancer risk posed by new chemicals (or new uses of old chemicals). For clarity, Table I ignores non-cancer risks, and also ignores non-dietary cancer risks; in practice EPA would of course consider all risks.[11]

BILLING CODE 6560-50-M

[11] Discussions in this document of risks resulting from pesticide use are limited to cancer risks due to dietary exposure. It is important for the reader to keep in mind that the Agency's reviews and decisions encompass many other risks as well. Table I proceeds from the assumption that all other risk criteria have been satisfied.

TABLE I—REGULATORY OUTCOMES UNDER OLD AND NEW POLICIES

CANCER RISK LEVEL	NEED 409 CLEARANCE?	ACTION UNDER FFDCA (NEW POLICY)	ACTION UNDER FIFRA (NEW POLICY)	COMPARISON TO PRIOR POLICY
No risk	No	Issue 408 tolerance	Register	Same
	Yes	Issue 408, 409 tolerances	Register	Same
Negligible cancer risk	No	Issue 408 tolerance	Register	Same
	Yes	Issue 408 409 tolerance	Register	Changed: under old policy, EPA would have refused to issue 408 issue 409 or register
Greater-than-negligible cancer risk	No	Issue 408 tolerance if benefit outweighs risk	Register if benefit outweighs risk	Same
	Yes	Refuse to issue 409 because of Delaney; refuse to issue 408 because 409 barred	Refuse to register because of lack of needed FFDCA clearances	Same

BILLING CODE 6560-50-C

The following sections discuss how the new approach will affect pesticides in various regulatory categories.

1. Pesticides That Have no Carcinogenic Effect or That Pose Only a Negligible Risk of Carcinogenicity

For pesticides that are the subjects of applications for intitial registration or for registration for new uses, and that either do not induce cancer in test animals or pose only a negligible human cancer risk (generally a quantitative risk of 10^{-6} or less), EPA will propose to establish section 408 tolerances and section 409 food additive regulations, where necessary, and thereafter to approve the applications for registration. Very little scrutiny will be given to the benefits of such non-carcinogenic or negligible-risk pesticides. As it has in the past, the Agency will assume the presence of benefits that outweigh the negligible risk. A list of pesticides that are potential candidates for consideration under the negligible-risk approach is provided in Appendix E.

2. Pesticides That Pose a Caracinogenic Risk That Is Greater Than Negligible

Some pesticides may pose a risk of carcinogenicity that is greater than negligible. Generally, such pesticides will be those with quantified upper-bound risks greater than 10^{-6}. (Some pesticides with quantified upper-bound risks greater than 10^{-6} may, however, fall into the negligible risk category for qualitative reasons, as discussed in Unit III.B.3.) For pesticide uses not requiring FFDCA section 409 clearances, EPA will continue its current practice of granting FIFRA registrations and the associated FFDCA section 408 tolerances for pesticides whose carcinogenic risk is greater than negligible only if the benefits are determined to outweigh the risks based on a careful scrutiny of the projected benefits compared to other available means of pest control. Benefits evaluations will be performed for such pesticides; the higher the risk, the more thorough the benefits evaluation that will be necessary. The risks of the available alternative pesticides will also be taken into account to determine if the total risk picture could be reduced by allowing the pesticide on the market. This approach accords with past practice.

But for the Delaney Clause, the Agency would propose to apply the same approach to pesticides in this category that require section 409 regulations. However, the Agency is not aware of any legal theory that would allow use of this approach under section 409 as it is currently written.

3. Treatment of Group C Chemicals

As explained in the EPA Guidelines for Carcinogen Risk Assessment, (51 FR 33992, September 24, 1986), there is great variability from one chemical to another in the amount and persuasiveness of evidence tending to show whether or not a chemical may cause cancer in humans. The EPA Guidelines represent the Agency's scheme for categorizing chemicals in terms of the weight of the evidence relating to their potential for human carcinogenicity. In general, the approach of the Guidelines is (1) to place a chemical in one of the groups (A through E) on the basis of the strength of the qualitative evidence of carcinogenicity from human epidemiology studies and animal tests and (2) for those chemicals showing some evidence of carcinogenicity, to set forth separately a quantitative upper bound on the risk that would be posed to humans if the substance in fact were a human carcinogen (see Appendix A). This information is useful to Agency officials and the public, since it provides a way to compare the risks of chemicals and to determine how consistently chemicals are regulated under the several statutory programs administered by the Agency.

The chemicals that pose the greatest difficulty in determining the proper regulatory response generally are those that fall into Group C ("possible human carcinogens") under the Guidelines. A chemical is placed in Group C if there is some evidence of potential carcinogenicity from animal studies, but that evidence is so limited that the chemical cannot be assigned to a higher category.

The Guidelines state that is some cases the Agency will not calculate a quantitative risk ceiling for a Group C chemical. Although it is always possible to calculate a quantitative risk number, the Agency believes that in some cases such quantitative estimates may suggest that the chemical definitely poses a risk to humans, even though in fact the Agency is quite unsure whether the chemical poses human risk. Appendix F lists a number of Group C pesticides and states whether quantitation of risk was deemed appropriate for each.

The Delaney Clause, of course, makes no provision for the weighing of animal-test evidence in terms of its pertience to human risk. If a chemical is found to induce cancer when ingested by animals or in other appropriate tests, the chemical is deemed "unsafe" under section 409 (unless the *de minimis* doctrine or one of the other previously-discussed exceptions applies). This absolute criterion presents special difficulties with respect to Group C pesticides.

The Agency's treatment for Delaney Clause purposes of a pesticide that falls in Group C will very. For example, many chemicals fall into Group C merely because the evidence of carcinogenicity comes from only one study. When the evidence from that study clearly indicates a carcinogenic effect in the animal tested, the Agency ordinarily treats the chemical as falling within the "high" end of the C category range and quantifies the risk. A tolerance decision for such a chemical will be based on the quantitative risk number, and the Delaney Clause will be deemed to apply unless the quantitative upper bound risk level is so low that the chemical's risk may be ignored under the *de minimis* doctrine. Conversely, a pesticide may be classified in Group C because the data on whether the chemical is an animal carcinogen are limited or uncertain, e.g., if the data are equivocal, unreliable, or subject to significant doubt, or if only benign tumors occurred. If the Agency determines that the weight of the evidence does not support treating the chemical as an animal carcinogen, the Agency will not treat the chemical as falling within the Delaney Clause bar. The Agency will, of course, in any such determination, set forth the reasons for its judgment. For example, a pesticide may be classified as belonging in Group C because the pesticide is associated with an increase in tumors in only one sex of one species with a lack of a clear dose/response relationship. Assuming that mutagenic data are negative and that structure/activity analysis shows no association with known carcinogens, the Agency generally would consider such a pesticide to be at the "low" end of the Group C range. It is doubtful that the Agency would require a quantification of the carcinogenic risk, and in such a case, the Delaney Clause would not be deemed applicable.

A pesticide may also fall into Group C, not because of any doubt about whether the chemical induces cancer in certain animal tests, but because of uncertainties as to the relevance of the finding to human risk. Reasons for questioning the relevance of the animal data to human risk could include, among other things, know variations in response between the test species and humans, or mechanistic considerations, e.g., a showing that cancer was induced in animals only as a secondly effect of an organic change in the animals induced by very high doses of the chemical and a showing that this effect would not occur at the low levels of human exposure. If a convincing

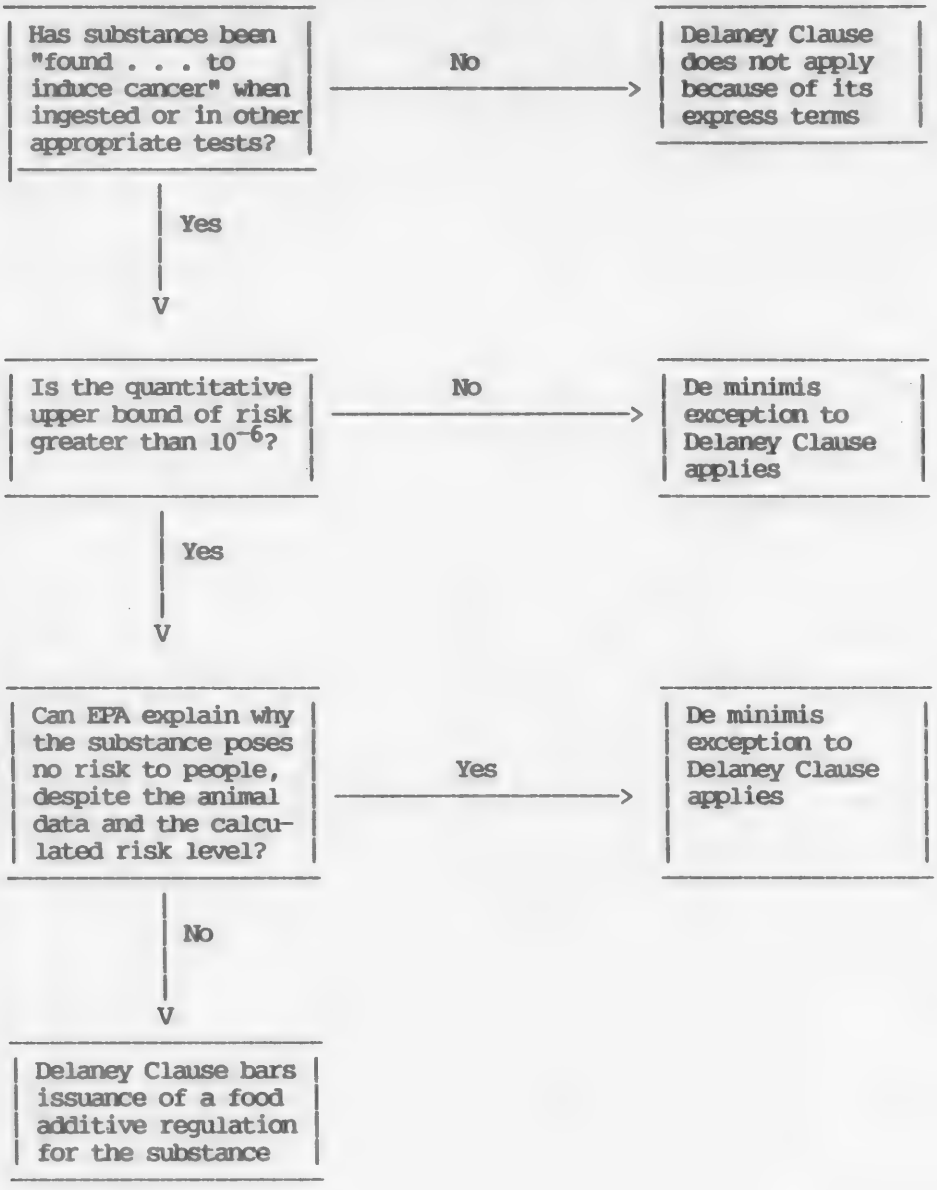
explanation exists for why the chemical poses no risk of cancer for humans, despite the fact that it has been shown to be an animal carcinogen in a feeding study or other appropriate study and has a theoretical upper bound risk greater than 10^{-6} calculated using a no-threshold model, EPA would propose to treat the chemical as falling into the negligible risk or *de minimis* category for Delaney Clause purposes because of the qualitative reasons for discounting the animal test results as a predictor of human risk. Given the limited knowledge about interspecies response differences and mechanisms of action for cancer, EPA anticipates that very few pesticides would qualify for *de minimis* treatment on this qualitative basis in the near future.

A Group C carcinogen would be regarded as subject to the Delaney Clause if it did not fall into the quantitative or qualitative *de minimis* exception described in this Notice.

The following Table II summarizes the Agency's proposed treatment of Group C carcinogens:

BILLING CODE [illegible]

TABLE II—DECISION SCHEME FOR GROUP C CHEMICALS


Has substance been "found . . . to induce cancer" when ingested or in other appropriate tests?
No
Delaney Clause does not apply because of its express terms
Yes
Is the quantitative upper bound of risk greater than 10^{-6}?
No
De minimis exception to Delaney Clause applies
Yes
Can EPA explain why the substance poses no risk to people, despite the animal data and the calculated risk level?
Yes
De minimis exception to Delaney Clause applies
No
Delaney Clause bars issuance of a food additive regulation for the substance

BILLING CODE 6560-50-C

If the Agency determines that the Delaney Clause does not apply to a pesticide despite limited evidence of the pesticide's oncogenicity, the Agency will examine all toxicological effects of possible concern in determining the limit of acceptable dietary exposure. The Agency will then determine the no-observed-effect level (NOEL) for the most sensitive effect, which in turn will be used in setting the allowable daily intake (ADI) used in calculating the maximum permissible level of residues. (See Appendix A of this document.)

4. Currently Registered Pesticides

EPA's position with respect to currently registered pesticides that pose at most a negligible dietary risk of cancer will parallel that described earlier for proposed new food uses of pesticides, and the regulatory status of registered pesticides that pose such risks will not be changed as a result of this Notice. At the other end of the spectrum, EPA is not changing its policy of attempting to cancel FIFRA registrations and revoke FFDCA clearances for pesticides that pose risks of cancer (or other adverse effects) that outweigh their benefits. Finally, EPA has not determined how to proceed with respect to a pesticide that poses an upper-bound cancer risk that is greater than negligible but that is outweighed by the benefits of the pesticide.

5. Section 18 Exemptions

Section 18 of FIFRA allows EPA to exempt State and Federal agencies from the provisions of the Act if the Agency finds that emergency conditions exist that warrant the exemption. The changes in the Agency's approach to the issuance of food additive regulations already described in this document would result in conforming changes in the implementation of the emergency exemption program. The Agency will apply the negligible risk standard in evaluating emergency exemption requests in a manner similar to other regulatory decisions concerning pesticides which are carcinogens. If associated dietary risks are greater than negligible, the Agency would consider granting the exemption only if the benefits are so great that they outweigh the risks. In this connection, EPA considers, among other things, whether use of the unregistered pesticide would present a lower dietary risk than currently registered alternatives.

Generally, an emergency exemption will not be granted if adequate progress is not being made toward full registration of the pesticide use. In the recent past, the Agency has treated the need for a section 409 tolerance as an automatic bar to a request for an exemption to allow emergency use of a substance that has been found to induce cancer in appropriate animal studies, on the assumption that no section 409 clearance could be issued and accordingly there would be no possibility of registration. In the future, however, the Agency will not consider the need for a 409 tolerance, *per se*, as blocking progress toward registration of such a pesticide. Rather it would consider whether it is likely the pesticide may subsequently be registered according to the policies outlined in this document.

6. Minor Uses

FIFRA directs the Agency to make the registration process more flexible for minor use pesticides. Use of the approaches set forth in this Notice should favor minor uses because they ordinarily involve lower exposures than uses of chemicals on major crops such as wheat or corn.

As with section 18 requests, the need for a section 409 tolerance will no longer be treated as an absolute bar to further consideration of a potentially carcinogenic minor use pesticide. In fact, a number of the pesticides listed in Table V of this document as eligible for reconsideration under the negligible risk standard are intended for minor uses.

IV. Response to the Third Recommendation of the NAS

The NAS has recommended that EPA focus on one major crop at a time and evaluate the risks posed by all the major pesticides registered for that crop rather than evaluating individual pesticides according to current procedures. The Agency's historical approach to reregistration has been to divide pesticides into "clusters" according to their predominant uses. A cluster is a group of chemicals and a group of sites that are closely correlated.

This approach was described in a **Federal Register** notice (45 FR 75488, November 14, 1980). The clusters were then ranked so that higher priority for review was given to those clusters that have significant use on food crops or were already known to pose special problems. Each individual pesticide chemical within the cluster is then evaluated, one at a time, for all of its uses. Thus, most of the major pesticides used on the 15 "high-consumption" crops identified by the NAS Report have had a recent comprehensive review or are scheduled for one in the near future. Appendix D of this document provides a status report on the Agency's review of 10 chemicals which have been identified as posing certain theoretical risks.

The NAS committee's recommended modification of EPA's approach is designed to ensure that final Agency decisions actually reduce dietary risk, help to preserve benefits of pesticide uses that pose low risks, and help to conserve limited Agency resources. The Agency agrees that this approach has merit in certain cases where the apparent risks are high and sufficient information is available to make comparative risk/benefit assessments. It also allows greater certainty that the final result will improve public health by comparing the risks and the benefits of the major alternatives at the same time.

Given the progress already made in the reregistration process, it is likey that the Agency will have the needed data on the major pesticides at approximately the same time so that comparative assessments can be done, at least for some crop/chemical combinations. During 1988, in fact, the Agency will be able to complete risk assessments for all but one of the six major fungicides (the exception is folpet, whose food use is relatively minor) and to compare the risks and benefits for these chemicals as recommended by the NAS.

There are, however, some problems associated with this approach. Timeliness will certainly be sacrificed in many cases. There will be more data to evaluate, and decisions will be more complex. Comparison of benefits may be difficult: available efficacy data are not designed to permit sophisticated benefits comparisons, and knowledge of all practical alternatives to a given pesticide may be limited and hard for the Agency to identify. For example, a pesticide might be effective for certain uses and yet might never have been registered for those uses because of a registrant's marketing strategy. Finally, it would not be advisable or protective of the public health to delay consideration of significant risks associated with a pesticide just because other pesticides used on the same crops cannot be evaluated at the same time due to the lack of key data. Consequently, the Agency expects to continue with its basic reregistration scheme for scheduling initial Registration Standards. However, adjustments will be made to allow consideration of alternatives whenever sufficient information is available and it appears to improve our ability to focus on high risk chemical/crop combinations.

Because of the Agency's basic priority scheme for Registration Standards, complete data bases for pesticides used on similar crops should be available at

roughly the same time, as in the case with the fungicides discussed in Appendix D. The sophistication of the comparative analyses may vary significantly, however, depending on the level of risk associated with the pesticide under review. In the case of cyanazine, for example, the final decision document discusses the known effects and the regulatory status of major alternatives briefly, but does not provide an extensive analysis because the Agency had concluded that the continued use of cyanazine did not pose unreasonable risks. It is likely, nevertheless, that the Agency will find it increasingly possible to make critical comparisons of pesticides which may substitute for each other.

V. Response to the Fourth Recommendation of the NAS

EPA is taking steps to implement the NAS recommendation to develop improved tools and methods to estimate more systematically the overall impact of prospective regulatory actions on health, the environment, and food production. A major new analytical tool that allows the Agency greater sophistication in the assessment of dietary risk is the computerized Tolerance Assessment System (TAS). TAS contains information on toxicology and residue date for particular pesticides, as well as food consumption information. Consumption information for various foods is based on a 1977–1978 nationwide survey of food consumption for different subgroups conducted by the U.S. Department of Agriculture (USDA). The TAS can be used to estimate dietary levels of pesticide residues for the average individual, as well as for 22 population subgroups, including various age and ethnic groups, infants, pregnant women, and nursing mothers. The system can also be used to differentiate overall consumption patterns by season and by region.

One option offered by the TAS is the calculation of separate TMRCs (Theoretical Maximum Residue Contribution, see Appendix A) for each of the 22 subgroups, based on the assumption that residues will be present at tolerance level and that 100 percent of the crop is treated. Alternatively, the TAS may be used to calculate an "Anticipated Residue Contribution" (ARC) where verifiable data are available on the actual distribution of residues on treated crops, the dissipation or concentration of residues during the storage, transport, and processing of food commodities, and/or the percentage of the total crop actually treated with a pesticide.

Since 1986, the TAS has been used to determine if there are particular dietary concerns for pesticides undergoing reevaluation in the Registration Standard Process, for new chemicals and new uses of old chemicals, and for any other pesticide for which the Agency has a special dietary concern.

To solicit guidance on the scientific criteria that EPA should consider in developing its policy regarding the use of the TAS, the Agency presented a paper entitled "Briefing Paper on the Tolerance Assessment System (TAS) for Presentation to the FIFRA Science Advisory Panel" to that Panel in March 1987 to address a number of specific issues. A copy of that paper and the Report of SAP Recommendations is available on request from the Office of Pesticide Programs. In particular, the Agency requested advice on the scientific criteria the Agency should consider for the use of population subgroups in a dietary exposure analysis, and for the use of percentiles of exposure within a particular population in estimations of dietary risk. The Agency also asked the Panel to address the appropriate margins of safety which the Agency should use for determining acceptable exposures for subgroups or percentiles of exposure within a subgroup. Finally, the Agency requested guidance on the scientific criteria that should be used in identifying appropriate residue levels for use in dietary exposure estimations, and on data presentation.

In response, the SAP noted that the TAS will enable the Agency to predict exposure levels for population subgroups with far greater precision than the current system and thus represents an improved approach. On the issue of the appropriate use of population subgroups, the Panel, noting that the focus of the TAS is on exposure rather than on toxicity, commented that calculations based on body weight, will tend to overstate the risk to infants where there is no toxicological basis for increased susceptibility. To correct for this factor, the Panel recommended that the Agency explore the use of body surface rather than body weight as a basis for comparison. On the safety factor issue, the Panel did not recommend any changes to the traditionally-used one-hundred fold safety factor. The Panel also suggested that the use of a controlled field study would be more likely to provide useful data for the TAS than monitoring data. Finally, the Panel recommended that data should be presented in such a way as to indicate the reliance of the approach on exposure, rather than on toxicity, and the Agency should indicate how relevance, biological significance, and other issues could be introduced into the process. The Agency will work to refine the TAS, as recommended by the Panel, and will seek to develop additional tools and methods to improve its risk/benefit assessment capabilities.

VI. Related Agency Activities

The Agency is working on a number of other initiatives and program improvements which are related to the issues discussed here.

A. FFDCA Section 408/409 Procedural Rules

The Agency has made considerable progress in developing consistent procedural rules pertaining to section 408 and 409 tolerances. Elsewhere in this issue of the **Federal Register**, the Agency is proposing new procedural rules for establishing, modifying, and revoking section 409 food additive regulations, as well as procedural rules governing the filing of objections, requests for hearings, and the holding of hearings under sections 408 and 409. These proposed rules not only will modernize out-of-date hearing rules, but also will restate and update practices that have not necessarily been codified. The next step in the regulatory process will be to expand the regulations to include (1) substantive interpretations and criteria for determining when tolerances and food additive regulations are required and what data are required in support of them and (2) the criteria and assumptions to be used by EPA in determining whether a tolerance or food additive regulation should be established, modified or revoked.

B. Encouraging Safer Pesticides

The Agency plans to take steps to encourage the development of safer pesticides. The Agency expects to publish a **Federal Register** notice detailing this plan in the near future.

C. Promoting Innovation in Pest Control

Despite gaps in current data bases, there are indications that human health and/or environmental risks exist for many currently registered nematicides and fungicides. In the case of nonfumigant nematicides, product efficacy depends largely on solubility. Solubility, however, increases soil mobility, giving rise to concern regarding ground and surface water contamination. Certain of the fumigant nematicides also are currently under Agency scrutiny because of potential chronic risks which may be incurred by workers. Of the registered fungicides, 12

are currently undergoing Special Review, and additional classes of fungicides may be placed in Special Review in the near future.

The Agency is working with the Agricultural Research Service and the Cooperative State Research Service to focus USDA research efforts on development of alternative controls for nematodes and plant disease. The Agency has identified a particular need for alternative controls for nematodes on citrus and potatoes and for plant diseases on tomatoes, grapes, leafy vegetables, and pome fruits. The Agency is also considering what incentives can be introduced into the registration process to encourage development of alternative controls. These may include waivers of tolerance fees and registration fees for new pesticides that fall into specified categories for which alternative controls are desirable.

The agency has also joined with USDA, FDA, and private industry to establish a National Pest Management Task Force. The Task Force will identify those pests of economic significance for which effective chemical controls are no longer available or for which little or no research or registration effort is underway. The Task Force will develop, in conjunction with member agencies and private associations, mechanisms fostering the development of acceptable control technologies.

D. Revision of Product Performance Guidelines

To improve the efficacy data base, the Agency is in the process of revising its Product Performance Guidelines to require the development of "comparative product performance data." In the past, product performance data requirements have concentrated on efficacy data that demonstrate how well a pesticide controls the pests listed on the label. The proposed revisions will require that registrants develop and maintain data which will provide information on performance of a pesticide compared to alternative pesticides, non-chemical techniques, and untreated controls.

E. Updating Food Consumption Data and Other TAS Improvements

Resources permitting, EPA hopes to update the food consumption data as part of our overall effort to implement TAS fully. Results of the latest USDA dietary survey should start coming in later this year, and the Agency plans to begin updating the TAS data in 1989. Subsequently, EPA hopes to update TAS every 10 years as results of a new USDA survey become available. The Agency also hopes to be able to enhance the analytical capabilities of TAS and to develop statistical guidelines and computer support for the incorporation of more accurate anticipated residue data based on actual residue studies.

F. Updating Animal Feed Data

Like human food consumption estimates, animal food consumption estimates also need updating. The Agency is currently working on a project to determine whether by-products from food processing plants are significant components of animal feeds. Once these significant feed items are identified, percent of diet figures for these new feed items will be determined.

G. Guidelines and Protocol Improvements

To provide for improved data for use in risk assessments, the Agency is developing guidelines and standard evaluation procedures for the use of registrants and food producers in the generation and submission of data to show actual pesticide residues in food. The Agency will also be working with the food industry to develop protocols for processing studies designed to show what happens to pesticide residues during processing.

H. Reclassification of Raw Versus Processed Commodities

The Agency intends to develop new criteria for classification of commodities as raw or processed in order to update and eliminate inconsistent 408/409 commodity classifications.

I. Factoring in Drinking Water Exposure to Pesticides

The Agency is concerned about human intake of pesticides via routes other than food, particularly drinking water. Historically, the Agency has based its decisions on tolerances only on dietary exposure from foods treated with pesticides. More recently the Office of Pesticides Programs (OPP) and the Office of Drinking Water (ODW) have begun focusing on drinking water as a potential source of pesticide residues in the diet. The Agency has recently made significant progress in its efforts to integrate activities or OPP and ODW with respect to pesticides in groundwater. All Health Advisories for pesticides in drinking water are now developed jointly by ODW and OPP, using the same data base and the same reference dose.

As a part of EPA's implementation of its Agricultural Chemicals in Groundwater Strategy, the Agency will be considering the extent to which pesticide residues in drinking water are a significant factor in dietary exposure to pesticide residues. This may be difficult in some cases, but is necessary in order to get a more complete picture of exposure. In cases where pesticides do reach drinking water supplies, it is necessary to factor this exposure into tolerance decisions.

For example, exposure to aldicarb through drinking water as a result of its presence in groundwater is being considered in the tolerance assessment in the special review of aldicarb. This is a case in which the data are available, and it is clear that drinking water is a potential route of exposure.

VII. Conclusion

In conclusion, the Agency believes that he recommendations of the NAS offer the Agency very useful guidance in improving and refining the process of evaluating pesticides for registration and tolerance purposes. Consistency between the criteria EPA uses in registering pesticides under FIFRA and in setting tolerances for pesticide residues on food under sections 408 and 409 of the FFDCA is a clearly desirable goal. A negligible risk approach to the pesticide regulatory process would allow the Agency to move in the direction of greater consistency, and allow the registration of new pesticides that pose lower risks than certain currently registered products.

The Agency also believes it would be desirable to have the authority to review all food additive regulations, as well as tolerances and registration actions, under a risk/benefit standard. Only by using a risk/benefit standard for all pesticide decisions will the Agency be able to achieve real consistency, and have the latitude to properly exercise its judgment based on a consideration of all relevant factors. Such an approach, over the long run, will be most likely to reduce the total risk attributable to pesticide use. As discussed in this document, the Agency cannot fully implement this goal without legislative change.

Nevertheless, the Agency will propose to follow the negligible-risk approach to the extent possible in future rulemakings on individual pesticides.

With regard to the other recommendations of the NAS, the Agency is focusing its energies on reviewing chemicals under a prioritization scheme in order to reduce risks attributable to pesticide use. Finally, the Agency is engaged in developing tools such as the Tolerance Assessment System to refine its ability to make regulatory decisions.

Dated: October 11, 1988.

Victor J. Kimm,

Acting Assistant Administrator, Office of Pesticides and Toxic Substances.

Appendix A—Procedures Followed by the Agency in Determining Allowable Residue Levels for Tolerances and Food Additive Regulations

In setting tolerances, EPA reviews residue chemistry data and toxicology data. The required data are essentially the same as those necessary to support the registration of a pesticide product used on food. To be acceptable, a tolerance level must be both high enough to cover residues likely to be left when the pesticide is used in accordance with its labeling, and low enough to be safe.

The Agency estimates the level of daily exposure which is not expected to cause appreciable risks during the human lifetime. With regard to risks other than cancer, this level is called the Accpetable Daily Intake (ADI) or Reference Dose (RfD). The ADI is calculated by dividing the no-observed effect level (NOEL) (the dosage level at which any adverse effects observed at higher dose levels are absent) from the most senstivie test showing adverse effects by an appropriate safety factor. This calculation is based on the concept that the risks of concern other than cancer are threshold effects—i.e., below the ADI there will be no adverse effect.

EPA also calculates the theoretical maximum residue contribution (TMRC), which represents the maximum amount of residue of a pesticide which a typical human could ingest by consuming food that bears the maximum level of the residue allowable under all existing and proposed tolerances. The TMRC is calculated by multiplying the tolerance level for each food by the amount of that in the typical American diet (according to available statistics on food consumption patterns) and totalling the values for all foods which may bear residues of that pesticide.

The TMRC is then compared with the ADI, and the tolerance is established (assuming no other concerns) if the TMRC is less than the ADI. A tolerance may be established in certain situations where the TMRC is higher than the ADI if residue data establish that the actual human exposure is not likely to exceed the ADI. For pesticides which may induce cancer, in addition to performing the ADI calculations discussed above for the effects of concern other than cancer, the Agency usually performs a quantitative risk assessment for the cancer risk. Cancer ordinarily is treated as a non threshold effect, because of a lack of evidence to refute the assumption that the carcinogenic response in humans to low doses is approximately proportional to the response in animals to high dose. Thus, some risk presumptively could result even at very low levels of exposure.

EPA's current carcinogencity testing scheme requires the use of several test doses (up to a level at or near the maximum tolerated dose) in at least two animal species, in order to magnify the likelihood of detection of a carcinogenic response in an economical, practically-sized animal test population (50 animals per sex per dose level) animal test population. At the present time, there is not better way to assess practically the potential carcinogenicity of a pesticide to which the entire U.S. population may be exposed. The animal data, and any available human epidemiology data, are assessed in accordance with EPA's "Cancer Assessment Guildelines, designed for use by all Agency programs in implementing a number of statutes designed to protect the public health, provide a qualititative classification scheme regarding human carcinogenicity based on a weight-of-the-eveidence analysis of the available data. Chemicals are classified into five groups, as follows:

1. Group A

Human Carcinogen: (Sufficient evidence of cancer causality from human epidemiologic studies).

2. Group B

Probable Human Carcinogen B1 limited evidence of carcinogenicity from human epidemiologic studies B2 sufficient evidence of carcinogenicity from animal studies.

3. Group C

Possible Human Carcinogen: Limited evidence of carcinogenicity in animals in the absence of human data, including malignant tumor response in a single well-conducted experiment not meeting conditions for sufficient evidence, tumor responses of marginal statistical significance in studies having inadequate design or reporting, benign tumors where short-term mutagenicity tests are negative, and responses of marginal statistical significance in a tissue with high background rate.

4. Group D

Not classifiable as to Human Carcinogenicity: Either inadequate evidence of carcinogenicity or absence of data.

5. Group E

Evidence of Non-Carcinogenicity for Humans: No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

A weight-of-the-evidence determination may involve consideration of, among other things, (1) the particular bioassay test system(s) used, (2) the evaluation of the histopathological and other results of the test(s), (3) the weight to be given to benign tumors, (4) mechanistic considerations, e.g., a situation where the chemical itself does not cause the tumor, but rather the effect the chemical causes at high doses of administration is the tumor-causing agent, and this effect would not occur at the lower doses of human exposure, and (5) the extent to which the overall quality and conduct of the tests accords with good laboratory practices.

Quantitative risk assessments are routinely performed for Category A and B carcinogens. In the case of pesticides classified as Category C, the Agency decides on a case-by-case basis whether the qualitative evidence is sufficient to warrrant a quantitative risk assessment, bearing in mind the possibility that publishing a risk number may create in the public mind an assumption of the reality of a risk to humans that is not supported by the qualitative data from animal studies.

To estimate the cancer risk posed by a pesticide from animal data, the Agency typically uses the linearized multistage model to extrapolate from the results seen at the high doses of the animal study to predict worst case risks at the much lower levels of estimated or actual human exposure. Using this model, a potency factor (Q_1*, called the "Q-star") is calculated from the 95 percent confidence limit of the slope of the linearized portion of the dose response curve. This potency factor represents a plausible, statistically-derived upper limit to the carcinogenic potency of the potential carcinogen at doses relevant to human exposure, and when multiplied by human exposure, yields an upper bound estimate of the risk. Such an estimate does not represent the actual risk, which may, in fact, be considerably lower or even as low as zero. Estimates of the upper limit on lifetime dietary risk from consumption of residues of a carcinogenic pesticide are calculated by multiplying the Q_1* by the average human dietary exposure, using food factors derived from USDA data on food consumption patterns. Unless data are available on the actual level of residues in particular food commodities, a worst-case risk will be calculated based on the assumption that all treated food bears

residues at the tolerance level and that 100 percent of the crops are treated.

EPA's current method of deriving these worst-case risk estimates for a carcinogenic chemical from animal data is based on somewhat more conservative premises than the approach of FDA. FDA assumes that humans and animals are equally sensitive to the test chemical on an equivalent body weight basis. EPA, on the other hand, bases its assessment on the premise that different sized animals are not equally sensitive to equal concentrations of a chemical, and makes a surface area adjustment to account for this difference.[1] The effect of this adjustment is to increase the estimate of human risk by about thirteen fold where data are derived from mice, and about 6½ fold when the data source is the rat as the test animal. Accordingly, EPA's risk numbers represent about an order of magnitude of risk greater than would be calculated using FDA methodology.

Appendix B—Food Use Pesticides With Evidence of Carcinogenicity

Active Ingredient	Group [1]	409 Tolerances food	409 Tolerances feed	Needs [2] 409 tolerances
1,3-dichloropropene [3,6].	B2			
2,4-D	D	x	x	
Acephate	C	x	x	
Acifluorfen	B2			x
Alachlor [6]	B2			x
Aliette (fosetyl al).	C			
Amdro	B2			
Amitraz	C			x
Arsenic acid (orthoarsenic acid).	A			
Asulam	C			
Atrazine	C			
Azinphos-methyl.	D			x
Benomyl [4]	C	x		
Bifenthrin [5]	C			
Bromacil				
Calcium arsenate.				
Captafol	B2			
Captan [6]	B2	x	x	
Chlordimeform & hydrochloride	B2			
Chlorobenzilate.				
Chlorothalonil.	B2			
Copper arsenate.				
Cypermethrin				
Cyromazine [4]			x	
Daminozide [6]	B2	x	x	
Diallate				
Dicamba [7]		x	x	
Dichlorvos (DDVP).	B2	x		
Diclofop methyl.				
Dicofol	B2	x		
Dimethipin (Harvade).	C			x
Dinoseb	C			
EDB	B2			
Ethalfluralin			x	
Ethylene oxide [6].		x		
Folpet	B2			
Gardona	C	x	x	
Glyphosate	D	x	x	
Lactofen [5]	B2			
Lead arsenate.				x
Lindane	D			x
Linuron [6]	C			
Mancozeb [4,6]	B2	x		
Magnesium arsenate.				
Maneb [4,6]	B2			x
Methanearsenic acid.			x	
Methidathion	C			x
Methomyl [4]				x
Metiram [4,6]	B2			
Metolachlor	C			
Oryzalin	C	x		
Oxadiazon	C			
O-phenylphenol.				
Paraquat	E	x	x	
Parathion	C			
PCNB (pentachloronitrobenzene).	D			
Permethrin				x
Phosmet	C	x		
Pronamide	C			
Propazine	C			
Propiconazole [5].	C			
P-dichlorobenzene [3].	C			
Sodium arsenate.				
Sodium arsenite.				
Terbutryn	C			
Tetrachlorvinphos.		x		
Thiodicarb [4]				x
Thiophanate methyl [4].				x
Toxaphene			x	
Triadimenol (Baytan).	C			
Tridiphane	C			
Trifluralin	C	x		
Zineb [4,6]	B2			

[1] Theoretically, this assumption is based on the premise that smaller animals, which eliminate heat from the body (an indication of metabolism) more efficiently than larger animals, are more efficient metabolically at detoxifying a chemical than larger animals. This difference in heat elimination has been related to the ratio of the surface area to the volume of the organism. Mathematically, the correction for surface area differences is made by dividing the dose in the animal study by the ratio of human body weight to test animal body weight to the two-thirds power.

Notes:

[1] Classification in accordance with EPA's Cancer Assessment Guidelines (see Appendix A) for those chemicals for which a weight-of-the-evidence determination has been made.

[2] Chemical has recently been determined to require a 409 tolerance.

[3] Registered uses (formerly not considered to be food uses) which have recently been defined as food uses.

[4] Included due to potentially oncogenic metabolite.

[5] Recently added to list because of newly registered food uses.

[6] Currently in Special Review for dietary concerns.

[7] Included because a contaminant is an oncogen.

Appendix C—Active Ingredients for Which Registration Standards Have Been Issued or are Scheduled for Next Year

Active Ingredient	Calendar year of issue
4-aminophyridine	1990
Acephate	1987
ADBAC	1985
Alachlor	1984
Aldicarb	1984
Aldrin	1986
Aliette (fosetyl al)	1983
	[1] 1988
Amitraz	1987
Amitrole	1984
Ammonium sulfamate	1981
	[1] 1989
Anilazine	1983
Arsenic acid (orthoarsenic acid)	1986
Aspon	1980
Asulam	1988
Atrazine	1983
	[1] 1989
Azinphos-methyl	1986
Bacillus thuringiensis	1988
Barium metaborate	1983
Bendiocarb	1987
Benefin	1989
Benomyl	1987
Bentazon/sodium bentazon	1985
Bifenox	1981
Bifenox (SRR)	1989
Bioallethrin	1988
BKLFI-2	1981
Boron (incl. borax & boric acid)	1983
Bromacil	1982
	[1] 1989
Bromoxynil	1989
Butonicarboxime	1981
Butylate	1983
	[1] 1989
Captafol	1984
Captan	1986
Carbaryl	1984
	[1] 1988
Carbofuran	1984
Carbophenothion	1984
Carboxin	1981
Chloramben	1981
	[1] 1989
Chlordane	1986
Chlordimeform hydrochloride	1985
Chlorobenzilate	1983
	[1] 1989

Active ingredient	Calendar year of issue
Chloroneb	1980
	[1] 1989
Chlorophacinone	1989
Chloropicrin	1982
Chlorpropham	1987
Chlorothalonil	1984
	[1] 1988
Chlorpyrifos	1984
	[1] 1989
Chlorsulfuron	1982
Chromated arsenicals	1986
Coal tar/creosote	1986
Copper chloride/nitrates	1987
Copper sulfate	1986
Coumaphos	1981
	[1] 1989
Cryolite	1983
	[1] 1988
Cyanazine	1984
Cycloate	1989
Cycloheximide	1982
Cyhexatin	1985
2,4-D	1988
2,4-DB	1988
2,4-DP	1988
Dacthal	1988
Dalapon	1987
Daminozide	1984
DCNA	1983
Deet	1980
Demeton	1985
Dialifor	1981
Diallate	1983
Diazinon	1988
3,5-dibromosalicylanilide	1985
Dicamba	1983
	[1] 1989
Dichlobenil	1987
Dichlone	1981
1,3-dichloropropene	1986
Dichlorvos (DDVP)	1987
Dicrotophos	1982
Difenzoquat	1988
Diflubenzuron	1985
Dimethoate	1983
	[1] 1989
Dioxathion	1983
Diphacinone	1989
Diphenamid	1987
Dipropetryn	1985
Diquat dibromide	1986
Disulfoton	1985
Diuron	1983
Dodine	1987
Endosulfan	1982
EPN	1987
EPTC	1983
	[1] 1989
Ethephon	1988
Ethion	1982
	[1] 1989
Ethoprop	1983
	[1] 1988
Ethoxyquin	1981
Ethyl parathion	1986
2-ethyl-1,3-hexanediol	1981
Fenamiphos	1987
Fenaminosulf	1983
Fenitrothion	1987
Fensulfothion	1983
Fenthion	1988
Fluchloralin	1985
Fluometuron	1985
Folpet	1987
Fonofos	1984
Formaldehyde	1986
Formetanate hydrochloride	1983
	[1] 1989
Fumarin	1980
Glyphosate	1986

Active ingredient	Calendar year of issue
Heliothis NPV	1984
Heptachlor	1986
Hexazinone	1982
	[1] 1988
Isocyanurates	1987
Isopropalin	1981
Lindane	1985
Linuron	1984
MCPA	1982
	[1] 1988
MCPB	1989
Magnesium & aluminum phosphide	1988
Malathion	1988
Maleic hydrazide	1988
Mancozeb	1987
Maneb	1988
Mecoprop	1989
Methiocarb	1987
Metalaxyl	1981
	[1] 1988
Metaldehyde	1989
Methamidophos	1982
Methidathion	1981
	[1] 1988
Methomyl	1982
	[1] 1988
Methoprene	1982
Methoxychlor	1989
Methyl bromide	1986
Methyl parathion	1986
Methylene bis thiocyanate	1989
Metiram	1988
Metolachlor	1980
	[1] 1987
Metribuzin	1985
Mevinphos	1988
Monocrotophos	1985
Monuron	1983
Monuron TCA	1983
Nabam	1987
Naled	1983
Napropamide	1989
Napthalene	1981
Naphthalene acetic acid & salts	1981
Naptalam	1985
Nitrapyrin	1985
Norflurazon	1984
	[1] 1989
OBPA	1981
O-phenylphenol	1989
Oryzalin	1987
Oxamyl	1987
Oxydemeton methyl	1987
Oxytetracycline	1988
Paraquat	1987
PCNB (pentachloronitrobenzene)	1987
Pendimethalin	1985
Perfluidone	1985
Phenmedipham	1987
Phorate	1984
Phorate (SRR)	1988
Phosalone	1981
	[1] 1987
Phosmet	1986
Phosphamidon	1987
Picloram	1985
	[1] 1988
Piperonyl butoxide	1989
Potassium bromide	1984
Potassium permanganate	1985
Prometryn	1987
Pronamide	1986
Propachlor	1985
Propanil	1987
Propargite	1986
Propazine	1989
Propham	1987
Resmethrin	1988
Rotenone	1988

Active ingredient	Calendar year of issue
Simazine	1984
	[1] 1989
Sodium & calcium hypochloride	1988
Sodium omadine	1985
Streptomycin	1988
Sulfur	1982
Sulfuryl fluoride	1985
Sulfotepp	1988
Sulprofos	1981
Sumithrin	1987
Tebuthiuron	1987
Temephos	1981
Terbacil	1982
	[1] 1989
Terbufos	1983
Terbutryn	1986
Terrazole	1980
	[1] 1989
Tetrachlorvinphos	1988
Thiophanate ethyl	1985
Thiophanate methyl	1988
Thiram	1984
TPTH	1984
Trichlorfon	1984
Trifluralin	1987
Trimethacarb	1985
Vendex	1987
Warfarin	1981
	[1] 1989
Zinc phosphide	1982

[1] Second round of review of the earlier registration standards.

Appendix D—Examples of Pesticide Chemicals With Tolerance Issues Currently or Recently Under Review

1. Benomyl

Benomyl is a broad spectrum systemic fungicide that controls a wide variety of plant diseases in field and vegetable crops, rice, tree fruit and nut crops, greenhouse, ornamentals, and turf sites. It is also used as a postharvest dip for fruits. In the Registration Standard issued for benomyl on March 31, 1986, the Agency concluded that benomyl and its major metabolite, 4-methyl benzimidazole carbamate (MBC), were possible human carcinogens (Group C), based on a significant increase in hepatocellular carcinomas in closely related strains of mice. Based on the established tolerances and the percent of crop treated, the Agency estimated any potential oncogenic risk from dietary exposure to be in the range of 10^{-5}. The Agency noted, however, that this quantitative assessment should not be accorded much weight since the evidence for oncogenicity is limited, but could be taken to represent a worst-case upper limit for risk. The Registration Standard also reassessed the residue data base supporting the established tolerance and food additive regulations for benomyl and concluded that additional data were required to fill the identified data gaps. A conclusion was also reached that additional food

additive regulations under section 409 may be required to cover residues in the processed fractions of citrus, tomatoes, grapes, and soybeans.

The additional residue data required by the Standard were received in the summer of 1987 and are under review. When general metabolism data (due July 1989) are received, EPA will be able to complete the tolerance reassessment for benomyl.

If the new data indicate that additional section 409 regulations are necessary, the Agency could establish such regulations under a de minimis approach if weight-of-the-evidence considerations lead to a conclusion that the risk to humans is negligible.

2. Captafol

Captafol, which was originally registered in 1962, is used as a fungicide on various vegetable and fruit crops. The Registration Standard for captafol, completed in September 1984, estimated a dietary risk of 10^{-4} based on tolerance levels, and required registrants to produce data on actual residues in food crops and additional oncogenicity data. A Special Review was also initiated. In early 1987, EPA classified captafol as a B2 (probable human) oncogen. The major registrant, Chevron Chemical Company, voluntarily cancelled its captafol registrations in March 1987. Formulators followed suit the next month. On August 22, 1988, the Agency terminated the Special Review because all registrations of captafol products had been cancelled. Also, the Agency plans to initiate action during 1989 to revoke the remaining tolerances for captafol.

3. Captan

Captan (N-trichloromethylthio-4-cyclohexane-1,2-dicarboximide) is a widely used agricultural fungicide, currently registered for use on a number of fruits and vegetables, small grains, cotton, grasses, flowers, and numerous household uses. The chemical has been the subject of a recent Registration Standard (issued in March 1986) and a Special Review. The Agency has found that the dietary intake of captan resulted in an increased incidence of uncommon adenomas and adenocarcinomas of the upper gastrointestinal tract in the Charles River CD–1 mouse, an increased incidence of these GI tumors in B6C3F1 mice, and a small dose-related increased incidence of kidney tumors in Charles River CD–1 rats. The Agency also noted positive mutagenic activity in gene mutation and chromosomal aberration assays, and a structural relationship to other compounds that demonstrated oncogenic effects.

In the Standard, the Agency requested residue data, including field trials to generate data for raw agricultural commodities treated at the maximum permitted rate, and studies to show the effect of washing, peeling, cooking, and processing on residue levels. Section 408 tolerances are currently established for a number of commodities which are subjected to processing, namely potatoes, soybeans, tomatoes, oranges, grapes, sweet corn, cottonseed, and pineapples. Section 409 tolerances for captan exist for washed raisins at 50 ppm (21 CFR 193.40; 21 CFR 193.40 redesignated as 40 CFR 185.500 at 53 FR 24666, June 29, 1988) and detreated corn seed at 100 ppm (21 CFR 561.65; 21 CFR 561.65 redesignated as 40 CFR 186.500 at 53 FR 24668, June 29, 1988). However, the 409 tolerance for detreated corn seed is in the process of being revoked for failure to submit supporting data. Section 409 tolerances must be set for some commodities, such as dried prunes and dry apple pomace.

In the Preliminary Determination of the Special Review, issued on June 2, 1985, the Agency determined that the dietary risk could be as high as 10^{-4} based on the assumption that residues are present at tolerance levels. The new data will allow the Agency to refine its risk assessment, and determine whether the currently established tolerances and food additive regulations should be revoked.

4. Chlordimeform

Chlordimeform was previously registered for a number of fruit and vegetable insecticide uses; however, most food uses were withdrawn by the registrants in 1976 because preliminary results of a mouse study suggested that chlordimeform caused malignant blood vessel tumors. In 1978, chlordimeform was registered for use on cotton with new restrictions to reduce applicator exposure. A Registration Standard was published for chlordimeform in January 1986, and the chemical has been referred to Special Review because of worker exposure concerns. In conducting the Registration Standard review, the Agency assessed dietary risks from the cotton use, using data on the percent of cotton crops actually treated (between 10 percent and 12 percent), and actual residue data showing chlordimeform residues ranging from 1 to 2 orders of magnitude lower than tolerance levels. Dietary risk from actual residues of chlordimeform occurring in commodities derived from treated cotton was estimated at 10^{-7}. Under the de minimis approach, the food additive regulations on commodities processed from cotton would be retained.

Very recently, the two registrants of the technical product have offered to voluntarily cancel the remaining cotton use, effective within the next year.

5. Chlorothalonil

Chlorothalonil is a fungicide used on numerous crops such as fruits, vegetables, and peanuts, as well as on ornamental turf. The chlorothalonil Registration Standard, issued in September 1984, identified significant data gaps; data have been submitted in response to the requirements set forth in the Standard. Based on such data, EPA has classified chlorothalonil as a B2 (probable human) oncogen. There are no existing 409 food additive regulations for this chemical; residue data required in the Standard will allow the Agency to determine if such regulations are necessary. A Revised Registration Standard and Tolerance Reassessment is scheduled for completion in September 1988. The Agency will assess during the Standard review whether the chemical should be referred to Special Review.

6. EBDCs

The EBDCs (ethylene bisdithiocarbamates) are a group of six fungicides (maneb, mancozeb, amobam, nabam, metiram, and zineb) with a common contaminant, metabolite, and degradation product called ethylene-thiourea (ETU). In 1984, a data call-in imposed extensive data requirements on the registrants of the EBDCs to enable the Agency to perform a comprehensive risk assessment. In response, registrants of amobam cancelled their products, and registrants of nabam deleted all food uses from their labels. Based on data received in response to the data call-in, the Agency has classified ETU and the EBDCs as B2 (probable human) oncogens. As set forth in the Registration Standard issued in April 1987, the dietary risk for mancozeb is estimated to be 10^{-4} based on actual residue data. The total dietary risks resulting from the use of all the EBDCs is likely to be higher. Residue data on maneb and metiram were received in March 1988. For zineb, which represents only 5 percent of total EBDC usage, residue data will not be available until 1991.

All the EBDCs have been placed in Special Review; the Preliminary Determination is scheduled for early 1989. The Agency expects to conduct a risk assessment of the dietary risk posed by these chemicals in the summer and fall of 1988, and then to conduct a comparative risk/benefit assessment of the major fungicides (EBDCs, captan,

chlorothalonil and benomyl) before making a regulatory decision on any one of them. As part of that review, the Agency will also determine what action to take with respect to the existing tolerances and food additive regulations. There are several food additive regulations for mancozeb, and data may indicate the need for such regulations for maneb, metiram, and zineb.

7. Folpet

Folpet is a broad spectrum fungicide which, in the past, has been used on both food and nonfood crops and as an industrial fungicide in the manufacture of coatings and plastics. Non-agricultural uses and home and garden uses have accounted for approximately 86 percent of its total usage. A Registration Standard was issued for folpet in June 1987, and additional residue data (due in 1991) were requested. Currently, all food uses have been suspended for failure to provide data. Current indications are that the only food use which is likely to be supported by data is the use on avocadoes.

The chemical has been classified as a B2 (probable human) oncogen. Prior to the recent suspensions, theoretical dietary risks, based on the assumption that residues would be present at tolerance levels, were in the 10^{-4} range, but the Agency believes that, if actual residue data and percent of crop treated were factored into the risk calculation, risks would be likely to be in the 10^{-6} range. There are no existing section 409 food additive regulations for folpet. If any food uses are reinstituted, and if residue data show that there is a concentration effect during processing, such regulations would be necessary. If the data indicate that the risk is in fact in the 10^{-6} range, the *de minimis* approach could be followed in establishing such regulations.

8. Linuron

Linuron, a herbicide used for pre- and post-emergent control of annual grasses and broadleaf weeds, was initially registered in 1966, and a number of tolerances have been established since then for its use on soybeans, corn, cotton, sorghum, wheat, asparagus, carrots, celery, parsnips, and potatoes. There are no section 409 food or feed additive regulations for linuron. However, the Agency has requested processing data to demonstrate whether the chemical does concentrate in processed commodities.

In 1984, a Registration Standard was issued for linuron and additional residue and chronic effects data required. At the time of the Standard, the Agency estimated dietary oncogenic risk in the range of 10^{-4} (based on residues at tolerance levels with some adjustment for percent of crop treated). However, since the time the Special Review was initiated, the Agency has issued its oncogenicity classification guidelines and has concluded that linuron is a group C (possible human) oncogen. Because only benign tumors are formed, these tumors occur only late in life, and there is no evidence of mutagenic activity, the Agency has concluded that linuron's human carcinogenic potential is low. Therefore the Agency has recently terminated the Special Review based on oncogenicity.

9. Permethrin

Permethrin is an insecticide first registered in 1979 for use on cotton, with a wide variety of other uses, including vegetables and pears (registered in 1982). The toxicology data base for permethrin is complete. The Agency has classified permethrin as a Group C oncogen, based on the induction of lung and liver tumors in female mice. Based on the very weak evidence of oncogenicity observed, the Agency determined that a quantitative risk assessment for this chemical is inappropriate because the likelihood of oncogenic effects in humans from low levels of permethrin is non-existent or extremely low. The Agency has, however, regulated this chemical as a possible oncogen for Delaney Clause purposes, and has declined to set 409 food additive regulations.

A tolerance for tomatoes, a commodity which is usually subject to processing, was established for Florida tomatoes, subject to a restriction that the tomatoes only be used for the fresh market. This approach was believed to be feasible for permethrin because of the unique circumstances of tomato production in Florida, i.e., 98 percent of the tomatoes were for the fresh market, and the limited number of canneries in the area agreed not to process tomatoes into a form which would result in concentrated residues (such as paste, puree, or ketchup). However, the Agency subsequently was informed that a cannery in Florida was processing permethrin-treated tomatoes into puree and paste. This incident demonstrates the impracticality of expecting growers and processors to distinguish between permethrin-treated tomatoes and untreated tomatoes.

In addition, the Agency is still seeking processing data to clarify whether residues will concentrate in any of the other processed commodities produced by Florida canneries. If the Agency were to follow the *de minimis* approach, permethrin would be a potential candidate for section 409 food additive regulations for additional uses in which concentration of the residues occurs during processing.

10. Trifluralin

Trifluralin is a selective preemergent herbicide registered for use on a variety of crops for the control of annual grasses and certain broad leaf weeds. This pesticide has been classified as a Group C carcinogen based on a significant increase in the incidence of malignant tumors of the renal pelvis, of the kidney and thyroid gland of male rats, and in the incidence of combined malignant and benign urinary bladder tumors in female rats at the highest dietary concentration tested. The Agency indicated in its August 1986 Registration Standard that processing data is being required for potatoes, sugar beets, soybeans, citrus fruits, sorghum, barley, corn and wheat grain, alfalfa hay, flax seed, cottonseed, peanuts, spent peppermint and spearmint hay, sugarcane, and sunflower seed. These data could indicate that additional food additive regulations are necessary to support current use patterns. Such regulations could be established under a *de minimis* approach if risks are found to be sufficiently low. Otherwise, if the Agency takes the approach that such regulations would be barred by the Delaney Clause, the corresponding section 408 tolerances might be subject to revocation, thereby eliminating many of the beneficial uses of this pesticide.

Appendix E—Candidates for Negligible Risk Consideration

Chemical	Type	Status	Proposed Use	Group
Aliette	Fungicide	New Use	Hops	C
Amitraz	Insecticide	New Use	Apples	C
Apollo	Insecticide	New Chemical	Apples	C
Cypermethrin corn	Insecticide	New Uses	Soybeans	C
Dicamba [1]	Herbicide	New Use	Cotton	Not classified.

Chemical	Type	Status	Proposed Use	Group
Glyphosate	Herbicide	New Use	Wheat	C/D
Harvade	Herbicide	New Use	Sunflowers	C
Methomyl [2]	Insecticide	New Use	Hops	Not classified.
Metolachlor	Herbicide	New Uses	Apples, flax, sunflowers	C
Permethrin corn	Insecticide	New Uses	Soybeans, apples, tomatoes	Treated as C
Savey	Insecticide	New Chemical	Apples	C
Verdict	Herbicide	New Chemical	Soybeans	In review

[1] A nitrosoamine contaminant of dicamba is an oncogen.
[2] Acetamide is an oncogen and an animal metabolite of methomyl.

Appendix F Group C Carcinogens' Status Re Risk Quantification

The decision as to whether or not quantification of risk for Group C chemicals is appropriate is subject to change as the Agency analyzes new data or reevaluate existing data. The following lists indicate those chemicals for which, as of August 1988, the Agency has determined a quantified risk number should or should not be used. There are a few other Group C chemicals for which this decision is still pending.

Risk Quantification Deemed Inappropriate

acephate
Aliette (fosetyl al)
amitraz
asulam
benomyl
bifenthrin
cypermethrin
dimethipin (Harvade)
fomesafan
gardona
linuron
methidathion
metolachlor
oryzalin
oxadiazon
parathion
permethion
phosmet
pronamide
propiconazole
triadimenol (Baytan)
tridiphane
trifluralin

[FR Doc. 88-24126 Filed 10-18-88; 8:45 am]
BILLING CODE 3198-01-M